

# **EXHIBIT “A”**

## **Pages 31-58**

journal advertisement for OxyContin.<sup>36</sup> FDA noted that among other problems, the advertisement implied that OxyContin had been studied for all types of arthritis pain when it had been studied only in patients with moderate-to-severe osteoarthritis pain, the advertisement suggested OxyContin could be used as an initial therapy for the treatment of osteoarthritis pain without substantial evidence to support this claim, and the advertisement promoted OxyContin in a selected class of patients—the elderly—without presenting risk information applicable to that class of patients.<sup>37</sup> Purdue agreed to stop dissemination of the advertisement. The second action taken by FDA was more serious. In January 2003, FDA issued a warning letter to Purdue regarding two professional medical journal advertisements for OxyContin that minimized its risks and overstated its efficacy, by failing to prominently present information from the boxed warning on the potentially fatal risks associated with OxyContin and its abuse liability, along with omitting important information about the limitations on the indicated use of OxyContin.<sup>38</sup> The FDA requested that Purdue cease disseminating these advertisements and any similar violative materials and provide a plan of corrective action. In response, Purdue issued a corrected advertisement, which called attention to the warning letter and the cited violations and directed the reader to the prominently featured boxed warning and indication information for OxyContin.<sup>39</sup> The FDA letter was one of only four warning letters issued to drug manufacturers during the first 8 months of 2003.<sup>40</sup>

In addition, in follow-up discussions with Purdue officials on the January 2003 warning letter, FDA expressed concerns about some of the information on Purdue's "Partners Against Pain" Web site. The Web site appeared to suggest unapproved uses of OxyContin for postoperative pain that may have been inconsistent with OxyContin's labeling and lacked risk

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<sup>36</sup>FDA indicated that in 2000, it issued 75 untitled letters to 46 drug manufacturers, as well as 4 warning letters to 4 drug manufacturers, for using promotional activities that violated the FD&C Act.

<sup>37</sup>The advertisement appeared in the *New England Journal of Medicine* in May 2000.

<sup>38</sup>The advertisements appeared in the *Journal of the American Medical Association* in October and November 2002.

<sup>39</sup>According to FDA, the corrective advertisement ran for 3 months and appeared in approximately 30 medical journals.

<sup>40</sup>FDA indicated that from January through August 2003, it issued 4 warning letters to four manufacturers and 12 untitled letters to seven drug manufacturers for using promotional activities that violated the FD&C Act.

information about the drug. For example, one section of the Web site did not disclose that OxyContin is not indicated for pain in the immediate postoperative period—the first 12 to 24 hours following surgery—for patients not previously taking the drug, because its safety in this setting has not been established. The Web site also did not disclose that OxyContin is indicated for postoperative pain in patients already taking the drug or for use after the first 24 hours following surgery only if the pain is moderate to severe and expected to persist for an extended period of time. Purdue voluntarily removed all sections of the Web site that were of concern to FDA.

FDA has also sent enforcement letters to other manufacturers of controlled substances for marketing and promotion violations of the FD&C Act. For example, in 1996, FDA issued an untitled letter to Zeneca Pharmaceuticals, at the time the promoter of Kadian,<sup>41</sup> for providing information about the drug to a health professional prior to its approval in the United States. Roxane Laboratories, the manufacturer of Oramorph SR, was issued four untitled letters between 1993 and 1995 for making misleading and possibly false statements. Roxane used children in an advertisement even though Oramorph SR had not been evaluated in children, and a Roxane sales representative issued a promotional letter to a pharmacist that claimed, among other things, that Oramorph SR was superior to MS Contin in providing pain relief. FDA has sent no enforcement letters to Ligand Pharmaceuticals concerning Avinza.

### **Purdue Distributed an OxyContin Video without FDA's Review That Appears to Have Made Unsubstantiated Claims and Minimized Risks**

Beginning in 1998, Purdue, as part of its marketing and promotion of OxyContin, distributed 15,000 copies of an OxyContin video to physicians without submitting it to FDA for review. This video, entitled *I Got My Life Back: Patients in Pain Tell Their Story*, presented the pain relief experiences of various patients and the pain medications, including OxyContin, they had been prescribed. FDA regulations require pharmaceutical manufacturers to submit all promotional materials for approved prescription drug products to the agency at the time of their initial use. Because Purdue did not comply with this regulation, FDA did not have an opportunity to review the video to ensure that the information it contained was truthful, balanced, and accurately communicated. Purdue has acknowledged the oversight of not submitting the video to FDA for

<sup>41</sup>Zeneca Pharmaceuticals promoted Kadian for Faulding Laboratories, the drug's manufacturer at that time.

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review. In February 2001, Purdue submitted a second version of the video to FDA, which included information about the 160-milligram OxyContin tablet. FDA did not review this second version until October 2002, after we inquired about its content. FDA told us it found that the second version of the video appeared to make unsubstantiated claims regarding OxyContin's effect on patients' quality of life and ability to perform daily activities and minimized the risks associated with the drug.

The 1998 video used a physician spokesperson to describe patients with different pain syndromes and the limitations that each patient faced in his or her daily activities. Each patient's pain treatment was discussed, along with the dose amounts and brand names of the prescription drugs, including OxyContin, that either had been prescribed in the past or were being prescribed at that time. The physician in the videos also stated that opioid analgesics have been shown to cause addiction in less than 1 percent of patients—a fact that FDA has stated has not been substantiated. At the end of the video, the OxyContin label was scrolled for the viewer.

In 2000, Purdue submitted another promotional video to FDA entitled *I Got My Life Back: A Two Year Follow up of Patients in Pain*, and it submitted a second version of this video in 2001, which also included information on the 160-milligram OxyContin tablet. Purdue distributed 12,000 copies of these videos to physicians. Both versions scrolled the OxyContin label at the end of the videos. FDA stated that it did not review either of these videos for enforcement purposes because of limited resources. Distribution of all four Purdue videos was discontinued by July 2001, in response to OxyContin's labeling changes, which required the company to modify all of its promotional materials, but copies of the videos that had already been distributed were not retrieved and destroyed.

FDA said that it receives numerous marketing and promotional materials for promoted prescription drugs and that while every effort is made to review the materials, it cannot guarantee that all materials are reviewed because of limited resources and competing priorities. FDA officials also stated that pharmaceutical companies do not always submit promotional materials as required by regulations and that in such instances FDA would not have a record of the promotional pieces.

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## Several Factors May Have Contributed to OxyContin Abuse and Diversion, but Relationship to Availability Cannot Be Assessed

There are several factors that may have contributed to the abuse and diversion of OxyContin. OxyContin's formulation as a controlled-release opioid that is twice as potent as morphine may have made it an attractive target for abuse and diversion. In addition, the original label's safety warning advising patients not to crush the tablets because of the possible rapid release of a potentially toxic amount of oxycodone may have inadvertently alerted abusers to possible methods for misuse. Further, the rapid growth in OxyContin sales increased the drug's availability in the marketplace and may have contributed to opportunities to obtain the drug illicitly. The history of abuse and diversion of prescription drugs in some geographic areas, such as those within the Appalachian region, may have predisposed some states to problems with OxyContin. However, we could not assess the relationship between the growth in OxyContin prescriptions or increased availability with the drug's abuse and diversion because the data on abuse and diversion are not reliable, comprehensive, or timely.

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## OxyContin's Formulation May Have Made It an Inviting Drug for Abuse and Diversion

While OxyContin's potency and controlled-release feature may have made the drug beneficial for the relief of moderate-to-severe pain over an extended period of time, DEA has stated that those attributes of its formulation have also made it an attractive target for abuse and diversion. According to recent studies, oxycodone, the active ingredient in OxyContin, is twice as potent as morphine.<sup>42</sup> In addition, OxyContin's controlled-release feature allows a tablet to contain more active ingredient than other, non-controlled-release oxycodone-containing drugs.

One factor that may have contributed to the abuse and diversion of OxyContin was FDA's original decision to label the drug as having less abuse potential than other oxycodone products because of its controlled-release formulation. FDA officials said when OxyContin was approved the agency believed that the controlled-release formulation would result in less abuse potential because, when taken properly, the drug would be absorbed slowly, without an immediate rush or high. FDA officials acknowledged that the initial wording of OxyContin's label was "unfortunate" but was based on what was known about the product at that time.

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<sup>42</sup>See, for example, G.B. Curtis, et al. "Relative Potency of Controlled-Release Oxycodone and Morphine in a Postoperative Pain Model," *European Journal of Clinical Pharmacology*, vol. 55, no. 6 (1999): 55:425-429.

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FDA officials told us that abusers typically seek a drug that is intense and fast-acting. When OxyContin was approved, FDA did not recognize that if the drug is dissolved in water and injected its controlled-release characteristics could be disrupted, creating an immediate rush or high and thereby increasing the potential for misuse and abuse. DEA officials told us that OxyContin became a target for abusers and diverters because the tablet contained larger amounts of active ingredient and the controlled-release formulation was easy for abusers to compromise.

The safety warning on the OxyContin label may also have contributed to the drug's potential for abuse and diversion, by inadvertently providing abusers with information on how the drug could be misused. The label included the warning that the tablets should not be broken, chewed, or crushed because such action could result in the rapid release and absorption of a potentially toxic dose of oxycodone. FDA places similar safety warnings on other drugs to ensure that they are used properly. FDA officials stated that neither they nor other experts anticipated that crushing the controlled-release tablet and intravenously injecting or snorting the drug would become widespread and lead to a high level of abuse.

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### OxyContin's Wide Availability May Have Increased Opportunities for Illicit Use

The large amount of OxyContin available in the marketplace may have increased opportunities for abuse and diversion. Both DEA and Purdue have stated that an increase in a drug's availability in the marketplace may be a factor that attracts interest by those who abuse and divert drugs. Following its market introduction in 1996, OxyContin sales and prescriptions grew rapidly through 2002. In 2001 and 2002 combined, sales of OxyContin approached \$3 billion, and over 14 million prescriptions for the drug were dispensed. (See table 2.) OxyContin also became the top-selling brand-name narcotic pain reliever in 2001 and was ranked 15th on a list of the nation's top 50 prescription drugs by retail sales.<sup>43</sup>

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<sup>43</sup>This information is from the National Institute for Health Care Management's Prescription Drug Expenditures reports for 2000 and 2001, prepared using American Institutes for Research analysis of Scott-Levin Prescription Audit Data. OxyContin was ranked 18th in 2000.

**Table 2: Total OxyContin Sales and Prescriptions for 1996 through 2002 with Percentage Increases from Year to Year**

Year	Sales	Percentage increase	Number of prescriptions	Percentage increase
1996	\$44,790,000	N/A	316,786	N/A
1997	125,464,000	180	924,375	192
1998	286,486,000	128	1,910,944	107
1999	555,239,000	94	3,504,827	83
2000	981,643,000	77	5,932,981	69
2001	1,354,717,000	38	7,183,327	21
2002	1,536,816,000	13	7,234,204	7

Sources: Purdue and IMS Health.

Legend: N/A = not applicable.

Note: GAO analysis of OxyContin sales and prescription data from Purdue and IMS Health, which includes data from all 50 states and the District of Columbia. Sales include combined retail and nonretail sales in drugstores, hospitals, and long-term-care facilities from the IMS Health U.S. National Sales database. Prescriptions include retail pharmacy, long-term-care, and mail-order prescriptions from IMS Health's National Prescriptions Audit.

## History of Prescription Drug Abuse in Some States May Have Predisposed Them to Problems with OxyContin

According to DEA, the abuse and diversion of OxyContin in some states may have reflected the geographic area's history of prescription drug abuse. The White House Office of National Drug Control Policy (ONDCP) designates geographic areas with illegal drug trade activities for allocation of federal resources to link local, state, and federal drug investigation and enforcement efforts. These areas, known as High-Intensity Drug Trafficking Areas (HIDTA), are designated by ONDCP in consultation with the Attorney General, the Secretary of the Treasury, heads of drug control agencies, and governors in the states involved.<sup>44</sup>

According to a 2001 HIDTA report,<sup>45</sup> the Appalachian region, which encompasses parts of Kentucky, Tennessee, Virginia, and West Virginia,

<sup>44</sup>In making a designation, ONDCP considers whether the geographic area is a center of drug production, manufacturing, importation, or distribution; whether state and local law enforcement agencies have committed resources to respond aggressively to the drug trafficking problem; whether drug activities in the area are having a harmful impact on other areas of the country; and whether a significant increase in federal resources is necessary to respond to the area's drug-related activities.

<sup>45</sup>Appalachia High Intensity Drug Trafficking Area Task Force, *The OxyContin Threat in Appalachia* (London, Ky.: August 2001).



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has been severely affected by prescription drug abuse, particularly pain relievers, including oxycodone, for many years. Three of the four states—Kentucky, Virginia, and West Virginia—were among the initial states to report OxyContin abuse and diversion. Historically, oxycodone, manufactured under brand names such as Percocet, Percodan, and Tylox, was among the most diverted prescription drugs in Appalachia. According to the report, OxyContin has become the drug of choice of abusers in several areas within the region. The report indicates that many areas of the Appalachian region are rural and poverty-stricken, and the profit potential resulting from the illicit sale of OxyContin may have contributed to its diversion and abuse. In some parts of Kentucky, a 20-milligram OxyContin tablet, which can be purchased by legitimate patients for about \$2, can be sold illicitly for as much as \$25. The potential to supplement their incomes can lure legitimate patients into selling some of their OxyContin to street dealers, according to the HIDTA report.

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**Limitations on Abuse and  
Diversion Data Prevent  
Assessment of the  
Relationship with  
OxyContin's Availability**

The databases DEA uses to track the abuse and diversion of controlled substances all have limitations that prevent an assessment of the relationship between the availability of OxyContin and areas where the drug is being abused or diverted. Specifically, these databases, which generally do not provide information on specific brand-name drugs such as OxyContin, are based on data gathered from limited sources in specific geographic areas and have a significant time lag. As a result, they do not provide reliable, complete, or timely information that could be used to identify abuse and diversion of a specific drug.

DEA officials told us that it is difficult to obtain reliable data on what controlled substances are being abused by individuals and diverted from pharmacies because available drug abuse and diversion tracking systems do not capture data on a specific brand-name product or indicate where a drug product is being abused and diverted on a state and local level. Because of the time lags in reporting information, the data reflect a delayed response to any emerging drug abuse and diversion problem. For example, the Drug Abuse Warning Network (DAWN) estimates national drug-related emergency department visits or deaths involving abused drugs using data collected by the Substance Abuse and Mental Health Services Administration (SAMHSA). The data are collected from hospital emergency departments in 21 metropolitan areas that have agreed to voluntarily report drug-abuse-related information from a sample of patient



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medical records, and from medical examiners in 42 metropolitan areas.<sup>46</sup> However, DAWN cannot make estimates for rural areas, where initial OxyContin abuse and diversion problems were reported to be most prevalent, nor does it usually provide drug-product-specific information, and its data have a lag time of about 1 year. DEA stated that development of enhanced data collection systems is needed to provide “credible, legally defensible evidence concerning drug abuse trends in America.”<sup>47</sup>

DEA relies primarily on reports from its field offices to determine where abuse and diversion are occurring. DEA officials stated that the initial areas that experienced OxyContin abuse and diversion problems included rural areas within 8 states—Alaska, Kentucky, Maine, Maryland, Ohio, Pennsylvania, Virginia, and West Virginia. In July 2002, DEA told us that it learned that OxyContin abuse and diversion problems had spread into larger areas of the initial 8 states, as well as parts of 15 other states, to involve almost half of the 50 states.<sup>48</sup> According to DEA officials, while DEA field offices continue to report OxyContin as a drug of choice among abusers, OxyContin has not been and is not now considered the most highly abused and diverted prescription drug nationally.<sup>49</sup> OxyContin is the most abused single-entity prescription product according to those DEA state and divisional offices that report OxyContin abuse.

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<sup>46</sup>The reliability of the data collected depends on whether the emergency room patient visit was reported as drug related, whether the patient reported taking a particular drug, and whether the emergency room physician indicated a drug’s brand name in the patient’s medical record.

<sup>47</sup>See app. III for more details on the abuse and diversion databases DEA uses.

<sup>48</sup>The 15 states are Alabama, Arizona, Colorado, Connecticut, Florida, Louisiana, Massachusetts, Mississippi, Missouri, New Jersey, North Carolina, South Carolina, Texas, Washington, and Wisconsin.

<sup>49</sup>Hydrocodone products, such as Anexsia, Hycodan, Lorcet, Lortab, and Vicodin, remain among the most abused and diverted scheduled prescription drugs nationally.

## Federal and State Agencies and Purdue Have Taken Actions to Prevent Abuse and Diversion of OxyContin

Since becoming aware of reports of abuse and diversion of OxyContin, federal and state agencies and Purdue have taken actions intended to address these problems. To protect the public health, FDA has strengthened OxyContin label warnings and requested that Purdue develop and implement an OxyContin risk management plan. In addition, DEA has stepped up law enforcement actions to prevent abuse and diversion of OxyContin. State Medicaid fraud control units have also attempted to identify those involved in the abuse and diversion of OxyContin. Purdue has initiated drug abuse and diversion education programs, taken disciplinary actions against sales representatives who improperly promote OxyContin, and referred physicians who were suspected of improperly prescribing OxyContin to the appropriate authorities. However, until fall 2002 Purdue did not analyze its comprehensive physician prescribing reports, which it routinely uses in marketing and promoting OxyContin, and other indicators to identify possible physician abuse and diversion.

## Reports of Abuse and Diversion Led to Label Changes and Other Actions by FDA

Reports of abuse and diversion of OxyContin that were associated with an increasing incidence of addiction, overdose, and death prompted FDA to revise the drug's label and take other actions to protect the public health. In July 2001, FDA reevaluated OxyContin's label and made several changes in an effort to strengthen the "Warnings" section of the label. FDA added a subsection—"Misuse, Abuse, and Diversion of Opioids"—to stress that physicians and pharmacists should be alert to the risk of misuse, abuse, and diversion when prescribing or dispensing OxyContin. FDA also added a black box warning—the highest level of warning FDA can place on an approved drug product. FDA highlighted the language from the original 1995 label—stating that OxyContin is a schedule II controlled substance with an abuse liability similar to morphine—by moving it into the black box. Also, while the original label suggested that taking broken, chewed, or crushed OxyContin tablets "could lead to the rapid release and absorption of a potentially toxic dose of oxycodone," a more strongly worded warning in the black box stated that taking the drug in this manner "leads to rapid release and absorption of a potentially *fatal* dose of oxycodone" (emphasis added). (See table 3.) In addition to the black box warning, FDA also changed the language in the original label that described the incidence of addiction inadvertently induced by physician prescribing as rare if opioids are legitimately used in the management of pain. The revised label stated that data are not available to "establish the true incidence of addiction in chronic patients."

**Table 3: Selected Language Approved by FDA in Warning Sections of OxyContin Labels, 1995 and 2001**

Warning label in 1995	Black box warning in 2001
<p>"Warning:</p> <p>OxyContin Tablets are to be swallowed whole, and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed OxyContin Tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone."</p>	<p>"Warning: OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine."</p> <p>"OxyContin Tablets are to be swallowed whole and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed OxyContin Tablets <b>leads</b> to rapid release and absorption of a potentially <b>fatal</b> dose of oxycodone." (emphasis added)</p>

Source: FDA-approved label for Purdue's OxyContin.

As mentioned earlier, the indication described in the original label was also revised to clarify the appropriate time period for which OxyContin should be prescribed for patients experiencing moderate-to-severe pain. The language in the 1995 label was changed from "where use of an opioid analgesic is appropriate for more than a few days" to "when a continuous, around-the-clock analgesic is needed for an extended period of time." (See table 4.) A summary of changes made by FDA to the original OxyContin label is given in appendix II.

**Table 4: Selected Language Approved by FDA in the Indication Sections of OxyContin Labels, 1995 and 2001**

Indication in 1995	Black box indication change in 2001
<p>"OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate-to-severe pain where use of an opioid analgesic is appropriate for more than a few days."</p>	<p>"OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate-to-severe pain <b>when a continuous, around-the-clock analgesic is needed for an extended period of time.</b>" (emphasis added)</p>

Source: FDA-approved label for Purdue's OxyContin.

Beginning in early 2001, FDA collaborated with Purdue to develop and implement a risk management plan to help identify and prevent abuse and diversion of OxyContin. As a part of the risk management plan in connection with the labeling changes, Purdue was asked by FDA to revise all of its promotional materials for OxyContin to reflect the labeling

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changes. In August 2001, FDA sent a letter to Purdue stating that all future promotional materials for OxyContin should prominently disclose the information contained in the boxed warning; the new warnings that address misuse, abuse, diversion, and addiction; and the new precautions and revised indication for OxyContin. Purdue agreed to comply with this request.

FDA officials told us that it is standard procedure to contact a drug manufacturer when the agency becomes aware of reports of abuse and diversion of a drug product so that FDA and the drug manufacturer can tailor a specific response to the problem. While FDA's experience with risk management plans is relatively new, agency officials told us that OxyContin provided the opportunity to explore the use of the plans to help identify abuse and diversion problems. FDA is currently making decisions about whether risk management plans will be requested for selected opioid products. Also, in September 2003, FDA's Anesthetic and Life Support Drugs Advisory Committee held a public hearing to discuss its current review of proposed risk management plans for opioid analgesic drug products to develop strategies for providing patients with access to pain treatment while limiting the abuse and diversion of these products.

FDA has also taken other actions to address the abuse and diversion of OxyContin. It put information on its Web site for patients regarding the appropriate use of OxyContin.<sup>50</sup> FDA worked with Purdue to develop "Dear Health Care Professional" letters, which the company distributed widely to health care professionals to alert them that the package insert had been revised to clarify the indication and strengthen the warnings related to misuse, abuse, and diversion. FDA also has worked with DEA, SAMHSA, the National Institute on Drug Abuse, ONDCP, and the Centers for Disease Control and Prevention to share information and insights on the problem of abuse and diversion of OxyContin.

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### DEA Developed an Action Plan to Deter OxyContin Abuse and Diversion

In April 2001, DEA developed a national action plan to deter abuse and diversion of OxyContin. According to DEA officials, this marked the first time the agency had targeted a specific brand-name product for monitoring because of the level and frequency of abuse and diversion associated with the drug. Key components of the action plan include coordinating enforcement and intelligence operations with other law

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<sup>50</sup>See [www.fda.gov/cder/drug/infopage/oxycontin/default.htm](http://www.fda.gov/cder/drug/infopage/oxycontin/default.htm).

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enforcement agencies to target people and organizations involved in abuse and diversion of OxyContin, pursuing regulatory and administrative action to limit abusers' access to OxyContin, and building national outreach efforts to educate the public on the dangers related to the abuse and diversion of OxyContin. DEA has also set Purdue's procurement quota for oxycodone at levels lower than the levels requested by Purdue.

DEA has increased enforcement efforts to prevent abuse and diversion of OxyContin. From fiscal year 1996 through fiscal year 2002, DEA initiated 313 investigations involving OxyContin, resulting in 401 arrests. Most of the investigations and arrests occurred after the initiation of the action plan. Since the plan was enacted, DEA initiated 257 investigations and made 302 arrests in fiscal years 2001 and 2002. Among those arrested were several physicians and pharmacists. Fifteen health care professionals either voluntarily surrendered their controlled substance registrations or were immediately suspended from registration by DEA. In addition, DEA reported that \$1,077,500 in fines was assessed and \$742,678 in cash was seized by law enforcement agencies in OxyContin-related cases in 2001 and 2002.

Among several regulatory and administrative actions taken to limit abusers' access to OxyContin and controlled substances, DEA's Office of Diversion Control, in collaboration with the Department of Justice's Office of Justice Programs, Bureau of Justice Assistance, provides grants to states for the establishment of prescription drug monitoring programs. The conference committee report for the fiscal year 2002 appropriation to the Department of Justice directed the Office of Justice Programs to make a \$2 million grant in support of the Harold Rogers Prescription Drug Monitoring Program, which enhances the capacity of regulatory and law enforcement agencies to collect and analyze controlled substance prescription data. The program provided grants to establish new monitoring programs in Ohio, Pennsylvania, Virginia, and West Virginia. California, Kentucky, Massachusetts, Nevada, and Utah also received grants to enhance existing monitoring programs.

DEA has also attempted to raise national awareness of the dangers associated with abuse and diversion of OxyContin. In October 2001 DEA joined 21 national pain and health organizations in issuing a consensus statement calling for a balanced policy on prescription medication use. According to the statement, such a policy would acknowledge that health care professionals and DEA share responsibility for ensuring that prescription medications, such as OxyContin, are available to patients who need them and for preventing these drugs from becoming a source of

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abuse and diversion. DEA and the health organizations also called for a renewed focus on educating health professionals, law enforcement, and the public about the appropriate use of opioid pain medications in order to promote responsible prescribing and limit instances of abuse and diversion. DEA is also working with FDA to encourage state medical boards to require, as a condition of their state licensing, that physicians obtain continuing medical education on pain management.

When OxyContin was first introduced to the market in 1996, DEA granted Purdue's initial procurement quota request for oxycodone. According to DEA, increases in the quota were granted for the first several years. Subsequently, concern over the dramatic increases in sales caused DEA to request additional information to support Purdue's requests to increase the quota. In the last several years, DEA has taken the additional step of lowering the procurement quota requested by Purdue for the manufacture of OxyContin as a means for addressing abuse and diversion. However, DEA has cited the difficulty of determining an appropriate level while ensuring that adequate quantities were available for legitimate medical use, as there are no direct measures available to establish legitimate medical need.

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### State Agencies Have Responded to Reports of OxyContin Abuse and Diversion

State Medicaid fraud control units and medical licensure boards have taken action in response to reports of abuse and diversion of OxyContin. State Medicaid fraud control units have conducted investigations of abuse and diversion of OxyContin, but generally do not maintain precise data on the number of investigations and enforcement actions completed. Although complete information was not available from directors of state Medicaid fraud control units in Kentucky, Maryland, Pennsylvania, Virginia, and West Virginia with whom we spoke, each of those directors told us that abuse and diversion of OxyContin is a problem in his or her state. The directors told us that they had investigated cases that involved physicians or individuals who had either been indicted or prosecuted for writing medically unnecessary OxyContin prescriptions in exchange for cash or sexual relationships.

State medical licensure boards have also responded to complaints about physicians who were suspected of abuse and diversion of controlled substances, but like the Medicaid fraud control units, the boards generally do not maintain data on the number of investigations that involved OxyContin. Representatives of state boards of medicine in Kentucky, Pennsylvania, Virginia, and West Virginia told us that they have received complaints from various sources, such as government agencies, health



care professionals, and anonymous tipsters, about physicians suspected of abuse and diversion of controlled substances. However, each of the four representatives stated that his or her board does not track the complaints by specific drug type and consequently cannot determine whether the complaints received allege physicians' misuse of OxyContin. Each of the four representatives also told us that his or her medical licensure board has adopted or strengthened guidelines or regulations for physicians on prescribing, administering, and dispensing controlled substances in the treatment of chronic pain. For example, in March 2001, the Kentucky Board of Medical Licensure adopted guidelines to clarify the board's position on the use of controlled substances for nonterminal/nonmalignant chronic pain.<sup>51</sup> The boards of medicine in Pennsylvania, Virginia, and West Virginia each have guidelines for the appropriate use of controlled substances that are similar to those adopted by Kentucky.

### **Purdue Is Implementing a Risk Management Plan for OxyContin**

In response to concerns about abuse and diversion of OxyContin, in April 2001 FDA and Purdue began to discuss the development of a risk management plan to help detect and prevent abuse and diversion of OxyContin. Purdue submitted its risk management plan to FDA for review in August 2001.<sup>52</sup> The plan includes some actions that Purdue proposed to take, as well as others that it has already taken. Purdue's risk management plan includes actions such as strengthening the safety warnings on OxyContin's label for professionals and patients, training Purdue's sales force on the revised label, conducting comprehensive education programs for health care professionals, and developing a database for identifying and monitoring abuse and diversion of OxyContin.

Under the risk management plan, OxyContin's label was strengthened, effective in July 2001, by revising the physician prescribing information and adding a black box warning to call attention to OxyContin's potential

<sup>51</sup>The Kentucky guidelines for the use of controlled substances in pain treatment provide that (1) a complete medical history and examination be conducted and documented in patient medical records, (2) a written treatment plan state objectives for determining treatment success, (3) the risks and benefits of the use of controlled substances be discussed by physician and patient, (4) periodic review of the course of treatment be conducted, (5) consultation or referral to an expert in pain management be considered for patients who are at risk for substance abuse, (6) patient's medical record be kept accurate and complete, and (7) physicians be in compliance with applicable federal and state controlled substance laws and regulations.

<sup>52</sup>Amended versions of Purdue's risk management plan for OxyContin were submitted to FDA for review in April 2002 and in March 2003.



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for misuse, abuse, and diversion. (See app. II.) Purdue trained its sales force on the specifics of the revised label and provided sales representatives with updated information on the appropriate use of opioid analgesics, legal guidelines associated with promotion of its products, and their responsibility and role in reporting adverse events. Purdue also reiterated to its sales representatives that failure to promote products according to the approved label, promotional materials, and applicable FDA standards would result in disciplinary action by the company. According to Purdue, from April 2001 through May 2003 at least 10 Purdue employees were disciplined for using unapproved materials in promoting OxyContin. Disciplinary actions included warning letters, suspension without pay, and termination.

Purdue also has provided education programs for health care professionals and the public under its risk management plan. For example, in 2001 Purdue supported seminars that examined ways health care professionals can help prevent abuse and diversion of opioids. Purdue worked with DEA and other law enforcement agencies to develop and implement antidiversion educational programs. In 2002, Purdue also launched the Web site [painfullyobvious.com](http://painfullyobvious.com) to educate teenagers, parents, law enforcement officers, and discussion leaders about the dangers of prescription drug abuse.

Because reliable data on the abuse and diversion of controlled substance drugs are not available, Purdue developed the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System, as part of its risk management plan, to study the nature and extent of abuse of OxyContin and other schedule II and III prescription medications and to implement interventions to reduce abuse and diversion.<sup>53</sup> According to Purdue, RADARS collects and computes abuse, diversion, and addiction rates for certain drugs based on population and determines national and local trends.

Since the launch of OxyContin, Purdue has provided its sales force with considerable information to help target physicians and prioritize sales contacts within a sales territory. Sales representatives routinely receive daily, weekly, monthly, and quarterly physician prescribing reports based

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<sup>53</sup>RADARS will collect information on brand-name and generic versions of buprenorphine, fentanyl, hydrocodone, hydromorphone, oxycodone, morphine, and methadone. Benzodiazepine is scheduled to be added to RADARS in late 2003.

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on IMS Health data that specify the physicians who have written prescriptions for OxyContin and other opioid analgesics, and the number of prescriptions written. Although this information has always been available for use by Purdue and its sales representatives, it was not until fall 2002 that Purdue directed its sales representatives to begin using 11 indicators to identify possible abuse and diversion and to report the incidents to Purdue's General Counsel's Office for investigation. Among the possible indicators are a sudden unexplained change in a physician's prescribing patterns that is not accounted for by changes in patient numbers, information from credible sources such as a pharmacist that a physician or his or her patients are diverting medications, or a physician who writes a large number of prescriptions for patients who pay with cash. As of September 2003, Purdue—through its own investigations—had identified 39 physicians and other health care professionals who were referred to legal, medical, or regulatory authorities for further action. Most of the 39 referrals stemmed from reports by Purdue's sales force.

Other actions included in the plan that were taken by Purdue prior to submission of its risk management plan include discontinuance of the 160-milligram tablet of OxyContin to reduce the risk of overdose from this dosage strength, the development of unique markings for OxyContin tablets intended for distribution in Mexico and Canada to assist law enforcement in identifying OxyContin illegally smuggled into the United States, and the distribution of free tamper-resistant prescription pads designed to prevent altering or copying of the prescription. Purdue also implemented a program in 2001 to attempt to predict "hot spots" where OxyContin abuse and diversion were likely to occur, but discontinued the program in 2002 when Purdue concluded that nearly two-thirds of the counties identified had no abuse and diversion.

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## Conclusions

At present, both federal agencies and the states have responsibilities involving prescription drugs and their abuse and diversion. FDA is responsible for approving new drugs and ensuring that the materials drug companies use to market and promote these drugs are truthful, balanced, and accurate. However, FDA examines these promotional materials only after they have been used in the marketplace because the FD&C Act generally does not give FDA authority to review these materials before the drug companies use them. Moreover, the FD&C Act provisions governing drug approval and promotional materials make no distinction between controlled substances, such as OxyContin, and other prescription drugs. DEA is responsible for registering handlers of controlled substances, approving production quotas and monitoring distribution of controlled

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substances to the retail level. It is the states, however, that are responsible for overseeing the practice of medicine and pharmacy where drugs are prescribed and dispensed. Some states have established prescription drug monitoring programs to help them detect and deter abuse and diversion. However, these programs exist in only 15 states and most do not proactively analyze prescription data to identify individuals, physicians, or pharmacies that have unusual use, prescribing, or dispensing patterns that may suggest potential drug diversion or abuse.

The significant growth in the use of OxyContin to treat patients suffering from chronic pain has been accompanied by widespread reports of abuse and diversion that have in some cases led to deaths. The problem of abuse and diversion has highlighted shortcomings at the time of approval in the labeling of schedule II controlled substances, such as OxyContin, and in the plans in place to detect misuse, as well as in the infrastructure for detecting and preventing the abuse and diversion of schedule II controlled substances already on the market.

Addressing abuse and diversion problems requires the collaborative efforts of pharmaceutical manufacturers; the federal and state agencies that oversee the approval and use of prescription drugs, particularly controlled substances; the health care providers who prescribe and dispense them; and law enforcement. After the problems with OxyContin began to surface, FDA and Purdue collaborated on a risk management plan to help detect and prevent abuse and diversion. Although risk management plans were not in use when OxyContin was approved, they are now an optional feature of new drug applications. FDA plans to complete its guidance to the pharmaceutical industry on risk management plans by September 30, 2004. The development of this guidance, coupled with FDA's current review of proposed risk management plans for modified-release opioid analgesics, provides an opportunity to help ensure that manufacturers include a strategy to monitor the use of these drugs and to identify potential problems with abuse and diversion.

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## Recommendation for Executive Action

To improve efforts to prevent or identify the abuse and diversion of schedule II controlled substances, we recommend that the Commissioner of Food and Drugs ensure that FDA's risk management plan guidance encourages pharmaceutical manufacturers that submit new drug applications for these substances to include plans that contain a strategy for monitoring the use of these drugs and identifying potential abuse and diversion problems.

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## Agency and Purdue Comments and Our Evaluation

We provided a draft of this report to FDA, DEA, and Purdue, the manufacturer of OxyContin, for their review. FDA and DEA provided written comments. (See apps. IV and V.) Purdue's representatives provided oral comments.

FDA said that it agreed with our recommendation that its risk management plan guidance should encourage all pharmaceutical manufacturers submitting new drug applications for schedule II controlled substances to include strategies to address abuse and diversion concerns. FDA stated that the agency is working on the risk management plan guidance. FDA also noted that the FD&C Act makes no distinction between controlled substances and other prescription drugs in its provisions regulating promotion, but that as a matter of general policy, the agency more closely scrutinizes promotion of drugs with more serious risk profiles. However, FDA does not have written guidance that specifies that promotional materials for controlled substances receive priority or special attention over similar materials for other prescription drugs. Furthermore, our finding that FDA did not review any of the OxyContin promotional videos provided by Purdue until we brought them to the agency's attention raises questions about whether FDA provides extra attention to promotional materials for controlled substances that by definition have a high potential for abuse and may lead to severe psychological or physical dependence. FDA recommended that we clarify our description of the content of the warning letter issued to Purdue and provide additional information describing the extent of the corrective action taken by Purdue. FDA also recommended noting in the report that part of the risk management plan in connection with the 2001 labeling changes was a requirement that all OxyContin promotional materials be revised to reflect the labeling changes and all future materials prominently disclose this information. Finally, FDA noted that the promotional videos discussed in the report were submitted by Purdue prior to the labeling change and discontinued as a result of the labeling change. As we note in the report, Purdue acknowledged that all the promotional videos were not submitted to FDA at the time they were distributed. Moreover, although Purdue told us that these videos were no longer distributed after the label change, those videos that had been distributed were not collected and destroyed. We revised the report to reflect FDA's general comments. FDA also provided technical comments that we incorporated where appropriate.

In its written comments, DEA agreed that the data on abuse and diversion are not reliable, comprehensive, or timely, as we reported. DEA reiterated its previous statement that Purdue's aggressive marketing of OxyContin fueled demand for the drug and exacerbated the drug's abuse and

diversion. DEA also stated that Purdue minimized the abuse risk associated with OxyContin. We agree with DEA that Purdue conducted an extensive campaign to market and promote OxyContin using an expanded sales force and multiple promotional approaches to encourage physicians, including primary care specialists, to prescribe OxyContin as an initial opioid treatment for noncancer pain, and that these efforts may have contributed to the problems with abuse and diversion by increasing the availability of the drug in the marketplace. However, we also noted that other factors may have contributed to these problems. We also agree that Purdue marketed OxyContin as having a low abuse liability, but we noted that this was based on information in the original label approved by FDA. DEA also acknowledged that the lack of a real measure of legitimate medical need for a specific product (OxyContin), substance (oxycodone), or even a class of substances (controlled release opioid analgesics) makes it difficult to limit manufacturing as a means of deterring abuse and diversion. DEA also noted that it is essential that risk management plans be put in place prior to the introduction of controlled substances into the marketplace, consistent with our recommendation. We revised the report to provide some additional detail on problems associated with OxyContin and Purdue's marketing efforts. DEA provided some technical comments on the draft report that we incorporated where appropriate.

Purdue representatives provided oral comments on a draft of this report. In general, they thought the report was fair and balanced; however, they offered both general and technical comments. Specifically, Purdue stated that the report should add the media as a factor contributing to the abuse and diversion of OxyContin because media stories provided the public with information on how to "get high" from using OxyContin incorrectly. Our report notes that the safety warning on the original label may have inadvertently alerted abusers to a possible method for misusing the drug. However, we note that the original label was publicly available from FDA once OxyContin was approved for marketing. Purdue also suggested that we include Duragesic, also a schedule II opioid analgesic, as a fourth comparable drug to OxyContin. The three comparable drugs we used in the report were chosen in consultation with FDA as comparable opioid analgesics to OxyContin, because they were time-released, morphine-based schedule II drugs formulated as tablets like OxyContin. In contrast, Duragesic, which contains the opioid analgesic fentanyl and provides pain relief over a 72-hour period, is formulated as a skin patch to be worn rather than as a tablet. Purdue representatives also provided technical comments that were incorporated where appropriate.

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We also provided sections of this draft report to the manufacturers of three comparative drugs we examined. Two of the three companies with a drug product used as a comparable drug to OxyContin reviewed the portions of the draft report concerning their own product, and provided technical comments, which were incorporated where appropriate. The third company did not respond to our request for comments.

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As agreed with your offices, unless you publicly announce this report's contents earlier, we plan no further distribution until 30 days after its issue date. At that time, we will send copies of this report to the Commissioner of Food and Drugs, the Administrator of the Drug Enforcement Administration, Purdue, and the other pharmaceutical companies whose drugs we examined. We will also make copies available to others upon request. In addition, the report will be available at no charge on the GAO Web site at <http://www.gao.gov>.

If you or your staffs have any questions about this report, please call me at (202) 512-7119 or John Hansen at (202) 512-7105. Major contributors to this report were George Bogart, Darryl Joyce, Roseanne Price, and Opal Winebrenner.



Marcia Crosse  
Director, Health Care—Public Health  
and Military Health Care Issues



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## Appendix I: Scope and Methodology

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To identify the strategies and approaches used by Purdue Pharma L.P. (Purdue) to market and promote OxyContin, we interviewed Purdue officials and analyzed company documents and data. Specifically, we interviewed Purdue officials concerning its marketing and promotional strategies for OxyContin, including its targeting of physicians with specific specialties and its sales compensation plan to provide sales representatives with incentives for the drug's sales. We also interviewed selected Purdue sales representatives who had high and midrange sales during 2001 from Kentucky, Pennsylvania, Virginia, and West Virginia—four states that were initially identified by the Drug Enforcement Agency (DEA) as having a high incidence of OxyContin drug abuse and diversion—and from California, Massachusetts, and New Jersey—three states that DEA did not initially identify as having problems with OxyContin. We asked the sales representatives about their training, promotional strategies and activities, and targeting of physicians. We also interviewed physicians who were among the highest prescribers of OxyContin regarding their experiences with Purdue sales representatives, including the strategies used to promote OxyContin, as well as their experiences with sales representatives of manufacturers of other opioid analgesics. We reviewed Purdue's quarterly action plans for marketing and promoting OxyContin for 1996 through 2003, Purdue's sales representative training materials, and materials from ongoing OxyContin-related litigation. To obtain information on how Purdue's marketing and promotion of OxyContin compared to that of other companies, we identified, in consultation with the Food and Drug Administration (FDA), three opioid analgesics that were similar to OxyContin. The three drugs—Avinza, Kadian, and Oramorph SR—are all time-released, morphine-based analgesics that are classified as schedule II controlled substances. We examined the promotional materials each drug's manufacturer submitted to FDA and any actions FDA had taken against the manufacturers related to how the drugs were marketed or promoted. We also interviewed company officials about how they marketed and promoted their respective drugs. Because of their concerns about proprietary information, the three companies did not provide us with the same level of detail about their drugs' marketing and promotion as did Purdue.

To examine factors that contributed to the abuse and diversion of OxyContin, we reviewed DEA abuse and diversion data as part of an effort to compare them with DEA's OxyContin state distribution data and with IMS Health data on the rates of OxyContin sales and prescription dispensing to determine if they occurred in similar geographic areas. We also analyzed the distribution of Purdue sales representatives by state and compared them with the availability of OxyContin and abuse and diversion



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**Appendix I: Scope and Methodology**

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data to determine whether states with high rates of OxyContin sales and prescription dispensing and abuse and diversion problems had more sales representatives per capita than other states. However, limitations in the abuse and diversion data prevent an assessment of the relationship between the availability of OxyContin and areas where the drug was abused and diverted. We also reviewed the High Intensity Drug Trafficking Area (HIDTA) reports on states with histories of illegal drug activities. We interviewed DEA and FDA officials, physicians who prescribed OxyContin, officials from physician licensing boards in selected states, officials from national health practitioner groups, and company officials and sales representatives about why OxyContin abuse and diversion have occurred.

To determine the efforts federal and state agencies and Purdue have made to identify and prevent abuse and diversion of controlled substances such as OxyContin, we interviewed FDA officials and analyzed information from FDA regarding the marketing and promotion of controlled substances, specifically OxyContin; FDA's decision to approve the original label for OxyContin; and FDA's subsequent decision to revise OxyContin's labeling, as well as FDA's role in monitoring OxyContin's marketing and advertising activities. We also interviewed DEA officials about the agency's efforts to identify and prevent abuse and diversion, including its national action plan for OxyContin, and how it determines the prevalence of OxyContin abuse and diversion nationally. We also interviewed officials from national practitioner associations, Medicaid fraud control units, and physician licensing boards in states with initial reports of abuse and diversion—Kentucky, Maryland, Pennsylvania, Virginia, and West Virginia—regarding concerns they had about the abuse and diversion of OxyContin. We reviewed Purdue's OxyContin risk management plan submissions to FDA from 2001 through 2003 to identify actions taken by Purdue to address abuse and diversion of OxyContin.

## Appendix II: Summary of FDA Changes to the Original Approved OxyContin Label

Table 5 provides a description of the changes made by FDA to sections of the original OxyContin approved label from June 1996 through July 2001. These changes included a black box warning, the strongest warning an FDA-approved drug can carry, and specifically addressed areas of concern related to the opioid characteristics of oxycodone and its risk of abuse and diversion.

**Table 5: FDA Changes to the Original OxyContin Label Made from June 1996 through July 2001**

Summary of FDA changes to original OxyContin label in 2001	Language in OxyContin label approved in 2001
Black box warning was added to stress the opioid nature of oxycodone and risks for abuse and diversion of the drug.	<p><b>"WARNING:</b></p> <p><b>OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.</b></p> <p>Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.</p> <p><b>OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.</b></p> <p>OxyContin Tablets are NOT intended for use as a prn analgesic. OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids. <b>OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE."</b></p>
<p><b>Clinical pharmacology</b></p> <p>—Provides a pharmacological description of oxycodone as a pure opioid agonist whose principal action is analgesia.</p> <p>—Identifies other members of the opioid agonist class, such as morphine, hydromorphone, fentanyl, and hydrocodone.</p> <p>—Describes the pharmacological properties of opioids in general (anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia).</p> <p>—Describes respiratory depression as one of the most serious side effects of opioids that could lead to overdose or death.</p>	<p><b>"CLINICAL PHARMACOLOGY</b></p> <p>Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression."</p>

**Appendix II: Summary of FDA Changes to the  
Original Approved OxyContin Label**

<b>Summary of FDA changes to original OxyContin label in 2001</b>	<b>Language in OxyContin label approved in 2001</b>
<p><b>Misuse, abuse, and diversion of opioids</b></p> <p>A subsection on misuse, abuse and diversion was added to the WARNINGS section of the label.</p> <p>—Characterizes oxycodone as an opioid agonist of the morphine-type and stresses that opioid agonists are sought by drug abusers and people with addiction disorders and are subject to diversion.</p> <p>—Makes clear that oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit, and that physicians and pharmacists should be aware of and alert to risk of misuse, abuse, and diversion when prescribing or dispensing oxycodone.</p> <p>—Modifies original label statement that iatrogenic addiction (addiction induced inadvertently by a physician or a physician's treatment) is rare if opioids were legitimately used in the management of pain to state that data are not available to establish the true incidence of addiction in chronic patients.</p>	<p><b>"Misuse, Abuse and Diversion of Opioids</b></p> <p>Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.</p> <p>Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.</p> <p>OxyContin has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see <b>WARNINGS</b> and <b>DRUG ABUSE AND ADDICTION</b>).</p> <p>Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.</p> <p>Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse of this product."</p>

**Appendix II: Summary of FDA Changes to the  
Original Approved OxyContin Label**

**Summary of FDA changes to original  
OxyContin label in 2001**

**Drug abuse and addiction**

- Emphasizes that the abuse potential of oxycodone is equivalent to that of morphine.
- Describes the controlled status of OxyContin and emphasizes that, like morphine and other opioids used in analgesia, oxycodone can be abused and is subject to criminal diversion.
- Stresses proper prescribing practices, dispensing, and storage.
- Deletes statement that delayed absorption of OxyContin was believed to reduce the abuse liability of the drug.
- Stresses the risks associated with parenteral injection of OxyContin and reiterates the original label's description of drug addiction and "drug-seeking" behaviors commonly in addicts and abusers.

**Language in OxyContin label approved in 2001**

**"DRUG ABUSE AND ADDICTION**

**OxyContin is a mu-agonist with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.**

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin, like other opioids, has been diverted for non-medical use. Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

**OxyContin consists of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV."**

**Safety and handling**

- Emphasizes the controlled status of OxyContin.
- Alerts health care professionals that OxyContin could be a target for theft and diversion and instructs that they should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of the product.

**"SAFETY AND HANDLING**

OxyContin Tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product."

Source: FDA-approved label for Purdue's OxyContin.

## Appendix III: Databases Used to Monitor Abuse and Diversion of OxyContin and Its Active Ingredient Oxycodone

DEA uses several databases to monitor abuse and diversion of controlled substances, including OxyContin and its active ingredient oxycodone. Specifically, the agency monitors three major databases—the Drug Abuse Warning Network (DAWN), the National Forensic Laboratory Information System (NFLIS), and the System to Retrieve Information from Drug Evidence (STRIDE).<sup>1</sup> DEA also monitors other data sources to identify trends in OxyContin abuse and diversion, such as the Substance Abuse and Mental Health Services Administration’s (SAMHSA) National Survey on Drug Use and Health, formerly the National Household Survey on Drug Abuse, and the Monitoring the Future Study funded by the National Institute on Drug Abuse.<sup>2</sup>

### DAWN Data

SAMHSA operates the DAWN system, which estimates national drug-related emergency department visits and provides death counts involving abused drugs. DAWN collects data semiannually on drug abuse from hospital emergency department admission and medical examiner data from 21 metropolitan areas and a limited number of metropolitan medical examiners who agree to voluntarily report medical record samples. The emergency department and medical examiner data generally do not differentiate oxycodone from OxyContin, unless the individual provides the information to the hospital or identifiable tablets are found with the person. Although samples from hospitals outside the 21 metropolitan areas are also available, DAWN is not able to make drug-related emergency department visit or death estimates for rural or suburban areas.

### NFLIS Data

NFLIS, a DEA-sponsored project initiated in 1997, collects the results of state and local forensic laboratories’ analyses of drugs seized as evidence by law enforcement agencies. NFLIS is used to track drug abuse and trafficking involving both controlled and noncontrolled substances and reports results by a drug’s substance, such as oxycodone, and not by its brand name. DEA stated that because new laboratories are being added,

<sup>1</sup>Other databases used by DEA to assess changes in drug abuse and diversion include the Drug Early Warning System, the Drug and Alcohol Services Information System, the Treatment Episode Data Set, the National Survey of Substance Abuse Treatment Services, the Uniform Facility Data Set, the Poison Control Center Data or Toxic Exposure Surveillance System, the Automation of Reports and Consolidated Ordering System, the DEA Theft System, and the DEA Field Reports and Investigative Teletypes.

<sup>2</sup>The National Institute on Drug Abuse is part of the National Institutes of Health within the Department of Health and Human Services.

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**Appendix III: Databases Used to Monitor  
Abuse and Diversion of OxyContin and Its  
Active Ingredient Oxycodone**

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its data should not yet be used for trending purposes. As of March 2003, 35 state laboratories and 52 local or municipal laboratories participated in the project.

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**STRIDE Data**

STRIDE, another DEA database, reports the results of chemical evidence analysis done by DEA laboratories in drug diversion and trafficking cases. Oxycodone data are reported by combining single and combination oxycodone drugs and do not provide specific enough information to distinguish OxyContin cases and exhibits. The database's lag time, which varies by laboratory, depends on how quickly the findings are entered after the seizure of the drug substance and its analysis.

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**National Survey on  
Drug Use and Health  
Data**

The National Survey on Drug Use and Health, another SAMHSA database, is used to develop national and state estimates of trends in drug consumption.<sup>3</sup> Prior to 2001, the self-reported survey asked participants if they had illicitly used any drug containing oxycodone. In 2001, the survey included a separate section for pain relievers, and asked participants if they had used OxyContin, identifying it by its brand name, that had not been prescribed for them. State samples from the survey are combined to make national- and state-level estimates of drug use, and because the estimated numbers derived for OxyContin are so small, it is not possible to project illicit OxyContin use on a regional, state, or county basis.

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**Monitoring the Future  
Survey Data**

The Monitoring the Future Survey, funded by the National Institute on Drug Abuse and conducted by the University of Michigan, annually monitors the illicit use of drugs by adolescent students in the 8th, 10th, and 12th grades. The 2002 survey included new questions using the brand names of four drugs, including OxyContin, in its survey on the annual and 30-day prevalence of drug use.

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<sup>3</sup>Self-reporting individuals are interviewed regarding their illicit drug use over three periods—within the last 30 days, during the past year, and during their lifetime. The survey data are limited, as it is not possible to determine specifically which year respondents may have used a drug illicitly, because they are asked both whether they have ever used the drug illicitly in their lifetime and whether they have used it during the past year.

## Appendix IV: Comments from the Food and Drug Administration



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

November 6, 2003

Marcia Crosse  
Director, Health Care-Public Health  
and Military Health Care Issues  
United States General Accounting Office  
441 G Street, NW  
Washington, DC 20548

Dear Ms. Crosse:

Please find the enclosed comments from the Food and Drug Administration on the GAO draft report entitled, PREScription DRUGS: Factors That May Have Contributed to OxyContin Abuse and Diversion and Efforts to Address the Problem, (GAO-04-110). The Agency provided technical comments directly to your staff.

We appreciate the opportunity to review and comment on this draft report before its publication as well as the opportunity to work with your staff in developing this report.

Sincerely,

A handwritten signature in black ink, appearing to read "Mark B. McClellan".

Mark B. McClellan, M.D., Ph.D.  
Commissioner of Food and Drugs

Enclosure



**Appendix IV: Comments from the Food and Drug Administration**

General Comments by the Department of Health and Human Service's Food and Drug Administration (FDA) on General Accounting Office's (GAO) Draft Report, *PRESCRIPTION DRUGS: Factors That May Have Contributed to OxyContin Abuse and Diversion Efforts to Address the Problem* (GAO-04-110)

FDA appreciates the opportunity to comment on GAO's draft report which focuses additional attention on the abuse and diversion of prescription drugs.

We have a few general comments regarding the overall report, as follows:

FDA's Regulation of Prescription Drugs

As currently written, GAO's draft report suggests that FDA decided as a matter of policy not to distinguish between types of drugs in regulating promotion. FDA believes it is important to clarify that the FD&C Act makes no distinction between controlled substances and other prescription drugs in its provisions regulating promotion, but that as a matter of general policy, the Agency more closely scrutinizes promotion of drugs with more serious risk profiles.

OxyContin Advertisements Violated the FD&C Act

FDA believes it is important to clarify the content of the warning letter issued to Purdue Pharma. In January 2003, FDA issued a warning letter to Purdue regarding two journal advertisements for OxyContin that minimized its risks and overstated its efficacy, by failing to present any information from the boxed warning on the potentially fatal risks associated with OxyContin and its abuse liability, along with omitting important information about the limitations on the indicated use of OxyContin. The FDA requested that Purdue cease disseminating these advertisements and any similar violative materials and provide a plan of corrective action.

We recommend that GAO include additional information describing the widespread dissemination of the corrective advertisement and the nature of its content, because we believe it gives important information on the extent to which complete and accurate information on OxyContin's risks and its limited indication was disseminated to healthcare providers this year resulting from the warning letter. This corrective advertisement ran for three months and appeared in approximately 30 medical journals. The three-paged advertisement, entitled "Important Correction of Drug Information," contained a two-paged spread, with a "Dear Healthcare Practitioner" letter on one side, which called attention to the warning letter and the cited violations, and directed the reader to the boxed warning and indication information for OxyContin prominently featured on the opposite side of the spread.

Reports of Abuse and Diversion Led to Label Changes and Other Actions by FDA

FDA recommends noting in the report that an important part of the risk management plan in connection with the 2001 labeling changes was that all OxyContin promotional materials be revised to reflect the labeling changes and all future promotional materials prominently disclose this information. As part of the risk management plan in connection with the labeling changes, Purdue was asked to revise all of its promotional materials for OxyContin to reflect the labeling changes. The FDA sent a letter to Purdue, dated August 3, 2001, stating that all future promotional materials for OxyContin should prominently disclose the information contained in the boxed warning, the new warnings that address misuse, abuse, diversion, and addiction, and the new precautions and revised indication for OxyContin. Purdue agreed to comply with this request in a letter dated August 7, 2001.

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**Appendix IV: Comments from the Food and  
Drug Administration**

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We also believe it is important to clarify that all three of the patient videos discussed in the report were submitted prior to the labeling change and discontinued as a result of the labeling change and these communications. As the discussion of these patient videos is currently written in the report, it could be misinterpreted that two of the patient videos were submitted after the labeling change as part of Purdue's modification of its promotional materials.

**Recommendation for Executive Action**

"To improve efforts to prevent or identify the abuse and diversion of schedule II controlled substances, the Commissioner of Food and drugs should ensure that FDA's risk management plan guidance encourages pharmaceutical manufacturers that submit new drug applications for these substances to include plans that contain a strategy for monitoring the use of these drugs and identifying potential abuse and diversion problems."

FDA agrees with GAO's recommendation and is currently working on the guidance.

## Appendix V: Comments from the Drug Enforcement Administration



U. S. Department of Justice  
Drug Enforcement Administration

[www.dea.gov](http://www.dea.gov)

NOV 05 2003

Ms. Marcia Crosse, Director  
Health Care-Public Health and  
Military Health Care Issues  
General Accounting Office  
441 G Street, N.W.  
Washington, D.C. 20548

Dear Ms. Crosse:

The Drug Enforcement Administration (DEA) submits the following comments on the facts and findings of the draft report, PRESCRIPTION DRUGS: *Factors that May Have Contributed to OxyContin Abuse and Diversion and Efforts to Address the Problem (GAO-04-110)*.

In general, the report is not as forthright as warranted on the causes/factors relating to the diversion of OxyContin. The root of the problem that this GAO report addresses appears to be the unfortunate convergence of Purdue's marketing techniques and the public/policy focus on pain undertreatment. The DEA has previously stated that the company's aggressive methods, calculated fueling of demand and the grasp for major market share very much exacerbated OxyContin's widespread abuse and diversion. While Purdue highlights its funding of pain-related educational programs and websites and its partnership with various organizations, the fact remains that Purdue's efforts—which may be viewed as self-serving public relations damage control—would not have been necessary had Purdue not initially marketed its product aggressively and excessively. Contributing to the abuse and diversion problem (and the product's excessive availability) is the fact that in promoting this drug to practitioners, Purdue deliberately minimized the abuse risk associated with OxyContin, as the report states on pages 21 and 35. The claim in Purdue's 'educational' video for physicians that opioid analgesics cause addiction in less than one percent of patients is not only unsubstantiated but also dangerous because it misleads prescribers.

In a further example of Purdue's pattern of aggressive pursuit of market share, the report states on page 31: "As part of its marketing campaign, Purdue distributed the usual types of branded promotional items to health care practitioners. Among these items were OxyContin fishing hats, stuffed plush animal toys, coffee mugs, compact discs..." In fact, the use of such branded promotional items for a Schedule II opioid is unprecedented. Distribution of promotional items such as hats, plush toys and coffee mugs is an indicator of Purdue's aggressive, excessive, and inappropriate marketing of their product, OxyContin. The DEA suggests the Department of Health and Human Services restrict promotional materials for Schedule II substances to items related to the practice of medicine or pharmacy.

Appendix V: Comments from the Drug  
Enforcement Administration

Ms. Marcia Crosse, Director

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Increased availability of controlled substances leads to increased opportunities for diversion. Therefore, it is essential that stringent risk management plans are put in place prior to the introduction of these products into the marketplace.

Unfortunately, there are limitations to DEA's ability to document the extent of diversion of specific products and DEA agrees with GAO's observation, on the bottom of page 36 of the draft report, that "data on abuse and diversion are not reliable, comprehensive, or timely." DEA also advocates the development of a system to provide "credible, legally defensible evidence concerning drug abuse trends in America," as stated on page 42 of the draft report. DEA included an additional \$750,000 in its 2003 budget request for an enhanced scientific data collection system that would include a National Medical Examiner Information System; however, this request has not been funded. This agency welcomes a recommendation by GAO that more reliable, comprehensive and timely databases be developed.

In addition, there are minor inaccuracies in this report, detailed below:

- First remark, ref page 3, 2nd full sentence of GAO draft report: DEA suggests the following edit to the draft report language (new/replacement language is in bold italics): "Unlike nonopioid pain relievers, ***OxyContin oxycodone, the active ingredient in OxyContin, has no known analgesic has no ceiling effect, that is, the dose amount a patient can take can be increased by the physician as needed to relieve pain. However, as the dose escalates, there is always a danger of serious side effects, including respiratory depression and death.***"
- Page 5, line 9: refers to "...three other opioid drugs, Avinza, Kadian, and Oramorph SR, that like OxyContin are classified as schedule II controlled substances." These drugs should be further identified as ***high dose extended release opioid drugs***, not simply "opioid drugs," here and throughout this document.
- Page 18, first paragraph: states "...a prescription for a schedule II drug may not be refilled, and the patient must see the practitioner again in order to obtain more drugs." While it is correct that schedule II drug prescriptions may not be refilled, a patient is not required to see the practitioner again but must obtain a new prescription.

Please correct the document language noted above to ensure the report's accuracy. The DEA appreciates the opportunity to provide comment to the GAO in these important matters.

Sincerely,



Rogelio Guevara  
Chief Inspector

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